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Long-term cardiovascular morbidity and mortality in patients treated for differentiated thyroid cancer

Short title: Cardiovascular morbidity in thyroid cancer

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Acknowledgements

This study was supported by research grants from the Finnish Cultural Foundation, Pirkanmaa Regional Fund and the Competitive Research Funding of the Special Responsibility Area of Tampere University Hospital. The authors thank Esko Väyrynen, M.A., for revising the language of the manuscript.

Summary

Objective Thyroid hormone suppression therapy has been widely used in the treatment of thyroid cancer, but concerns have been raised about the cardiovascular risks of this treatment. The objective of this study was to evaluate long-term cardiovascular morbidity and mortality in patients treated for differentiated thyroid cancer (DTC) and to assess the effect of TSH suppression and radioiodine (RAI) treatment on the cardiovascular outcome.

Design Retrospective cohort study

Patients and Measurements Patients (n=901) treated for DTC between 1981-2002 at two Finnish University hospitals were compared with a randomly chosen reference group (n=4485) matched for age, gender and the place of residence. Kaplan-Meier and Cox regression analyses were used to estimate the risk of morbidity or death due to different cardiovascular diseases (CVD) after the diagnosis of DTC.

Results Morbidity due to any CVD (hazard ratio [HR] 1.16, 95% confidence interval [CI] 1.05-1.28) and due to all arrhythmias (HR 1.25, CI 1.06-1.48) and atrial fibrillation (HR 1.29, CI 1.06-1.48) was more frequent in the DTC patients than in the controls. The increased cardiovascular morbidity was confined to patients with a mean TSH level below 0.1 mU/l (HR 1.27, CI 1.03-1.58), and to those treated with RAI (HR 1.18, CI 1.06-1.32). Cardiovascular mortality, however, was lower among the patients than the controls (HR 0.73, CI 0.58-0.92), due to a lower mortality from coronary artery disease.

Conclusions DTC patients have an increased CVD morbidity, which is mostly accountable to atrial fibrillation, and to TSH suppression below 0.1 mU/l.

Key words Cardiovascular Diseases, Atrial Fibrillation, Thyroid Neoplasms, Thyroid Hormones, Iodine Radioisotopes, Follow-Up Studies, Mortality

Introduction

Differentiated thyroid cancer (DTC) includes papillary and follicular thyroid cancer and represents over 90 % of all thyroid cancers detected (1). The incidence of thyroid cancer has increased over the past few decades; in the US the incidence has nearly tripled between the years 1975-2009 (2,3). The increasing incidence of thyroid cancer has been explained by early diagnosis leading to a growing number of small papillary thyroid cancers, which have an excellent prognosis (2,3). The increased use of neck area imaging may reveal incidental thyroid cancers with no effect on survival (4,5). Despite the increased incidence, mortality from thyroid cancer has remained stable (2).

Diagnosis of small low-risk tumours may expose the patients to aggressive cancer treatment, which may have unfavourable long-term effects (3). Thyroid hormone suppression therapy (THST) by levothyroxine has been traditionally used as a treatment of thyroid cancer to improve the outcome, but recently the necessity and safety of this treatment in low-risk patients has been questioned (6,7). There are concerns about the long-term cardiovascular effects of THST-induced iatrogenic thyrotoxicosis (6,7), as the risks of endogenous hyperthyroidism are well known (8).

Increased cardiovascular mortality and an increased risk of atrial fibrillation (AF) have been reported among DTC patients (9-12). An association between a low TSH level and an increased risk of cardiovascular mortality has been found in patients treated for DTC (9). THST has been reported to increase myocardial strain, left ventricular mass, and diastolic dysfunction, to impair arterial elasticity, and to induce prothrombotic changes in DTC patients (13-16). The most recent guidelines on DTC recommend weighing the potential benefits of THST against the possible harms of stringent TSH suppression (17-19). For the

time being, the appropriate degree of TSH suppression remains unsettled, and there are discrepancies between different guidelines (17-19).

The aim of this study was to evaluate the long-term cardiovascular morbidity and mortality in DTC patients. The secondary aim was to assess the effect of the TSH suppression level and radioiodine (RAI) treatment on the cardiovascular outcome of the patients.

Materials and Methods

In this retrospective study, all the patients treated for DTC between 1981 and 2002 at two Finnish University Hospitals (Tampere and Oulu University Hospital, responsible for the specialized health care of 16 % of the Finnish population) were included. Details of this cohort have been recently described in a study analyzing the risk of second cancer after the treatment of DTC (20). In short, this study included 920 consecutive patients, most of whom had a total thyroidectomy (78 %) and were subsequently treated with RAI (81 %). Of the patients, 493 were treated at Tampere University Hospital and 427 at Oulu University Hospital. Nineteen patients and their corresponding controls were excluded because of missing information, errors in the identification numbers, or limitations regarding data release. For each patient, five controls were chosen from the Population Register Center of Finland, individually matched for age, gender, and the place of residence. Controls diagnosed with thyroid cancer (n=12) during the follow-up were excluded.

Follow-up of the patients started on the date of DTC diagnosis and on the same date for the corresponding controls. The follow-up regarding cardiovascular morbidity ended on the date of the first cardiovascular disease (CVD) -associated outpatient visit or

hospitalization, date of death, date of emigration, or the common closing date (31.12.2014), whichever occurred first. Information regarding the treatment of DTC patients was collected from the medical records of the two participating hospitals.

Cardiovascular morbidity was evaluated on the basis of hospital visits at any Finnish hospital due to CVD during the follow-up. Information on CVD–associated hospital visits was obtained from the nationwide Hospital Discharge Registry (HILMO), which is maintained by the National Institute of Health and Welfare (THL). This registry includes the inpatient hospital admissions of all Finnish residents since 1969 and the outpatient hospital visits since 1996. The hospitalization or outpatient visit was included in the analyses, if the primary or one of the two first secondary diagnoses at discharge was a cardiovascular disease, according to the International Classification of Diseases (ICD). Between 1969 and 1986 the ICD-8 codes 400-458 were included, between 1987 and 1995 the ICD-9 codes 400-459, and from the year 1996 on, the ICD-10 codes I10-99 were included.

The CVD diagnoses were categorized into nine main groups (21): hypertension, coronary artery disease, diseases of the pulmonary circulation, arrhythmias, heart failure, cerebrovascular disease, diseases of the arteries and veins, valvular diseases and cardio-myopathies. In the group of arrhythmias, AF was also studied separately. First, morbidity due to any CVD was evaluated. Then, morbidity because of the different CVD subgroups was analysed separately, regardless of any morbidity due to other CVD diagnoses. Only the first hospitalization or outpatient visit due to a given CVD disease was included in the analysis.

Data on the causes and time of death were obtained from Statistics Finland, and information on emigration from the Population Registration Centre. The underlying cause of death was used in the mortality analyses. Information from the separate registers was

linked together by using the unique personal identification number assigned to all Finnish residents.

The ethics committee of the Pirkanmaa Hospital District approved the study protocol (study number R15144). The National Institute of Health and Welfare, Statistics Finland, the Population Register Centre, and the University Hospitals yielded permission for the use of data from their registers. The Declaration of Helsinki was obeyed during the study.

Statistical analysis

The statistical analyses were performed with the IBM SPSS Statistics version 24.0 (IBM Corp. Released 2016). Unpaired t test was used to compare the mean age during the first hospital visit due to a CVD between the patients and the controls. Mann-Whitney U test was used to compare the median follow-up times. Kruskall Wallis test was used to compare the age and the cumulative dose of RAI between the three TSH groups. The cumulative rate of CVD-associated hospital visits, overall mortality and cardiovascular mortality were compared between the patients and the controls by using Kaplan-Meier curves and the log-rank test.

The data on all the TSH measurements performed during the study period were available on the patients treated at Tampere University Hospital. The association between the TSH level and the CVD outcome was analyzed by using a geometric mean (9) of all available TSH measurements after the diagnosis of DTC. The geometric mean TSH level was categorized into three groups, according to the American Thyroid Association recommendation (below 0.1 mU/l, 0.1 to 0.5 mU/l, and above 0.5 mU/l). TSH values below the detection limit were given the numeric value of the detection limit of the TSH

117 method (for example <0.01 mU/l was assumed as 0.01 mU/l). The doses of RAI
118 treatments were obtained from the medical records of both hospitals.
119 Three different kinds of Cox regression analyses were performed. The first analysis
120 included all the DTC patients and controls, and the hazard ratios (HR) and 95%
121 confidence intervals (95% CI) were estimated for morbidity and mortality due to different
122 CVDs after the diagnosis of DTC. Prevalent CVD was used as a covariate in the analysis to
123 adjust for CVD morbidity before the start of the follow-up.
124 In the second analysis, hazard ratios for morbidity due to any CVD were determined in
125 the following subgroups of patients and their corresponding controls: age (< 40 years, 40-
126 59 years and ≥ 60 years), gender, geometric mean TSH level during follow-up (<0.1 mU/l,
127 0.1 to 0.5 mU/l and >0.5 mU/l) and RAI treatment status (yes, no).
128 The third analysis included only the DTC patients and it was performed to evaluate the
129 effect of the different patient- and treatment-associated factors on the risk of CVD
130 morbidity. The covariates used were gender, age, prevalent CVD, TSH level (per 1 mU/l
131 increase) and cumulative RAI dose (per 100 mCi increase). This analysis included only the
132 patients treated at Tampere University Hospital, because the TSH data was available only
133 regarding these patients.
134 The analyses were repeated with a subdistribution hazards model, in which the
135 competing event of death in the analysis of cardiovascular morbidity, and the competing
136 event of non-cardiovascular death in the analysis of cardiovascular mortality were taken
137 into account. The subdistribution hazards ratios were calculated with the statistical
138 software Stata for Windows version 13.0 (StataCorp, College Station, TX, USA).

Results

A total of 901 DTC patients and 4485 controls were included in the study, and 81% of them (n=733) were female (Table 1). The mean age at the time of DTC diagnosis was 48 (standard deviation [SD] 16) years. Most of the patients 79% (n=709) had papillary cancer, 11% (n=97) had follicular cancer, and 10% (n=95) had a follicular variant of papillary thyroid cancer. The number of the study subjects and their CVD-associated hospital visits are shown in Figure 1. The median follow-up time was 18.8 (interquartile range [IQR] 14.4-23.5) years in the DTC patients and 19.0 (IQR 15.1-23.4) years in the controls (p=0.391). A cancer recurrence was recorded in 15% (n=134) of the patients. During the follow-up 28% of the patients (n=250) and 28% of the controls (n=1237) died.

Morbidity due to any CVD (HR 1.16, 95% CI 1.05-1.28) was increased among the DTC patients compared with the controls (Figure 2, Panel a and Table 2). The results did not change when the subjects with a prevalent CVD were excluded or when the subdistribution hazards model was used. During the follow-up, 53% (n=478) of the patients and 48% (n=2134) of the controls were treated for a CVD. The mean age during the first treatment due to any CVD was 63.0 (SD 13.8) years in the patients and 64.7 (SD 14.2) years in the controls (p=0.014). The median time from the beginning of the follow-up to the first treatment due to any CVD was 9.0 (IQR 4.2-14.8) years in the patients and 9.4 (IQR 4.0-15.3) years in the controls (p=0.512).

When the different CVDs were studied separately, the risk of all arrhythmias (HR 1.16, 95% CI 1.06-1.48) and AF (HR 1.29, 95% CI 1.06-1.57) was increased among the DTC patients, compared to the controls (Figure 2, Panel b-c and Table 2). The results did not change when the subjects with prevalent arrhythmias or prevalent AF were excluded, or when the subdistribution hazards model was used. During the follow-up, 13% of the

patients and 11% of the controls were treated for AF. The mean age of the DTC patients during the first treatment for AF was 70.3 (SD 12.0) years and 73.1 (SD 11.2) years for the controls (p=0.015). The median time from the beginning of the follow-up to the first treatment due to AF was 13.1 (IQR 7.3-16.6) years for the patients and 13.1 (IQR 7.7-18.8) years for the controls (p=0.440).

In the subgroup analysis, morbidity due to any CVD was increased in patients under 40 years of age (HR 1.27, 95% CI 1.00-1.60) and also in patients aged 40 to 59 years (HR 1.23, 95% CI 1.07-1.43), compared with the corresponding controls. The risk tended to increase also in patients aged 60 or over (HR 1.17, 95% CI 0.99-1.38). Female patients had an increased risk of hospital treatments due to any CVD compared with their controls (HR 1.14, 95% 1.02-1.28).

There was no difference in the overall mortality (HR 0.98, 95% CI 0.85-1.12) between the DTC patients and the controls (Figure 3, Panel). Cardiovascular mortality, however, was lower among the patients than the controls (HR 0.73, 95% CI 0.58-0.92), which was accountable to a lower mortality from coronary artery disease among the patients (HR 0.69, 95% CI 0.50-0.95) (Figure 3, Panel b, Table 3, supplements). The result remained unchanged when the subdistribution hazards model was used.

AF was recorded as an underlying cause, a contributory cause or the direct cause of death in 5% (n=13) of the patients and 6% (n=77) of the controls (p=0.535). The most common CVD cause of death was coronary artery disease, which was the underlying cause of death in 17% (n=42) of the patients and 25% (n=315) of the controls. Of the DTC patients, 7.7% (n=69) died of the thyroid cancer. Among the deceased DTC patients, 28% (n=69) died of the thyroid cancer, 32% (n=81) of a CVD and 40% (n=100) from other causes. In the control group, 43% (n=533) died of a CVD and 57% (n=704) from other causes.

Altogether 11292 TSH measurements from 469 patients were available for the analyses. Of the TSH measurements, 5068 (45%) were below the detection limit. The median number of TSH measurements per patient during the follow-up was 23 (interquartile range [IQR] 14-33).

The patients in the different TSH groups differed regarding the age at DTC diagnosis ($p<0.001$). The median age of patients with a geometric mean TSH level below 0.1 mU/l was 44.6 (IQR 34.7-52.6) years vs. 51.4 (IQR 40.4-67.5) years in the patients with TSH between 0.1 and 0.5 mU/l, and 60.1 (IQR 49.2-70.2) years in the patients with TSH above 0.5 mU/l. Also, the cumulative dose of RAI differed between the TSH groups ($p=0.005$). Among patients who did not receive RAI a greater proportion (27%, n=36) had TSH above 0.5 mU/l compared with patients who received RAI (16%, n=53).

In the subgroup analysis, the patients with a geometric mean TSH level under 0.1 mU/l had an increased risk of CVD morbidity (HR 1.27, 95% CI 1.03-1.58), compared with the corresponding controls (Figure 4, Panel a-c). The risk also tended to increase in patients with a mean TSH > 0.5 mU/l (HR 1.31, 95 % CI 0.98-1.77), but not in those with a TSH level between 0.1 and 0.5 mU/l (HR 1.04, 95 % CI 0.83-1.31). These results did not change when the TSH values above 30 mU/l were excluded.

Of the DTC cohort, 81% (n=732) were treated with RAI ablation. The median cumulative dose of RAI was 100 mCi (IQR 100-150 mCi). In the subgroup analysis, the patients treated with RAI ablation had an increased risk of CVD morbidity (HR 1.18, 95% CI 1.05-1.31) compared to the corresponding controls, contrary to the patients not treated with RAI vs. their respective controls (HR 1.07, 95% CI 0.85-1.34) (Figure 4, panels c-d).

In the Cox regression analysis including only the patients, age (HR 1.05, 95% CI 1.04-1.06), male gender (HR 1.62, 95% CI 1.19-2.22) and a prevalent CVD at the time of DTC diagnosis (1.68, 95% CI 1.25-2.24) predicted morbidity due to any CVD, whereas the TSH

level or the cumulative dose of RAI did not have a statistically significant effect on CVD morbidity.

Discussion

To our knowledge, this is the largest study evaluating cardiovascular morbidity and mortality among DTC patients with a long follow-up time. This study is also the first one to report the risk of other cardiovascular diseases in addition to AF in DTC. We found that the risk of hospital treatment due to any cardiovascular disease is increased among patients treated for DTC, compared with age- and gender-matched control group. The increased risk is mostly accountable to an increased risk of AF.

Based on previous studies, the survival rate of patients diagnosed with a DTC is excellent (3). No difference in the all-cause mortality was found between the patients with DTC, and the matched control group in the present study, either. Given the similar life expectancy compared with the general population, the co-morbidities, the quality of life, and the burden of the cancer treatments should be taken into account, in addition to the risk of cancer recurrence. Studies on endogenous subclinical and clinical hyperthyroidism indicate an increased risk of cardiovascular morbidity and mortality (8,21,22). Findings from endogenous thyroid disease, however, cannot be generalised on thyroid cancer patients, because endogenous and exogenous thyrotoxicosis are not entirely comparable conditions, and they may impose different risks on the cardiovascular system (11,23).

Previous studies on DTC patients have reported an increased incidence of AF, but no association between the TSH level and AF incidence, although such an association is known to exist in endogenous hyperthyroidism (24,25). Abonowara et al. (11) found an increased prevalence of AF among 136 thyroid cancer patients, but no correlation

between the level of TSH and the occurrence of AF. Klein Hesselink et al. (10) also reported an increased risk of AF among 518 DTC patients, but there was no association between the TSH level and the risk of AF, whereas the cumulative dose of RAI was associated with a slightly increased AF risk. No difference in the risk of AF was found in a cohort of 771 thyroid cancer patients with suppressed (TSH ≤ 0.4 mU/l) versus those with non-suppressed (> 0.4 mU/l) TSH concentrations (12). In our study patients with a mean TSH level below 0.1 mU/l had an increased CVD risk compared with the corresponding controls. The risk tended to increase also in the patients with TSH above 0.5 mU/l, but the difference was not statistically significant. Previously, a U-shaped relationship between thyroid hormone concentrations and cardiovascular parameters has been reported in DTC patients studied during exogenous thyrotoxicosis, euthyroidism and hypothyroidism, both ends of the range showing similar effects on myocardial mechanical properties (13).

In contrast to our results indicating decreased cardiovascular mortality, Klein Hesselink et al. in 2013 reported a significantly increased risk of cardiovascular and all-cause mortality in 524 DTC patients during an 8.5-year follow-up, and the risk was independent of age, sex and cardiovascular risk factors (9). A low TSH level was associated with increased cardiovascular mortality, but the cumulative RAI dose was not. Other studies, however, do not indicate increased cardiovascular mortality in DTC patients (26,27). Eustatia-Rutten et al. in 2006 found that the number of non-thyroid cancer-related deaths in T1–3M0 DTC patients were lower compared with age- and sex-matched cohort of the general population (26). In our study, the cardiovascular mortality was lower among the patients than controls. If a DTC patient dies of thyroid cancer, he/she cannot reach the endpoint of a cardiovascular or another non-thyroid cancer-related death, which may underestimate the risk of cardiovascular death in the DTC cohort (26). In this study cardiovascular mortality remained lower among the patients

than among the controls, when the competing event of non-cardiovascular death was taken into account.

One explanation for the lower cardiovascular mortality among the DTC patients might be the lifelong follow-up of DTC patients, during which cardiovascular risk factors may be revealed and treated earlier, compared with the general population (26). Hypothyroidism is related to hypercholesterolaemia, atherosclerosis and an increased risk of coronary artery disease (28). In contrast to hypothyroidism, exogenous subclinical thyrotoxicosis might have beneficial effects, protecting from coronary artery disease.

In our study, the death certificate data from Statistics Finland, and the underlying cause of death was used for both the patients and the controls. In Finland the registration of an underlying cause of death is mandatory. Also, the entry of diagnosis codes to HILMO is mandatory when a patient is discharged from a hospital. Therefore, the high quality and completeness of the data obtained from these nationwide registers are a significant strength of this study. (29) Previous studies indicate that the validity of CVD diagnoses in these registers is high (29,30).

However, the register-based study method has limitations. The HILMO register includes only visits in the specialized health care system, which may underestimate the incidence of non-severe cardiovascular diseases among both the patients and the controls. Technical errors in the entry of CVD diagnosis codes or misdiagnosis of the CVDs are possible. However, all the DTC diagnoses were confirmed when the information was collected from the medical records of the hospitals. CVDs might have been diagnosed more likely among the DTC patients, because of the lifelong follow-up of DTC, which could overestimate the risk of CVD morbidity of the DTC patients.

A limitation is that we did not have information on cardiovascular risk factors, such as smoking, diabetes, or body mass index. Also, we did not have information on the

prevalence of endogenous thyroid disorders among the controls, nor did we have information on the use of levothyroxine or antithyroid drugs. Both hyperthyroidism and hypothyroidism have been found to increase cardiovascular morbidity. Regardless of the possibility of thyroid disorders among the control group, the risk of cardiovascular morbidity was increased among the DTC patients.

Because of the retrospective study method, conclusions cannot be drawn about the causality between DTC treatment and CVD morbidity, i.e., whether the increased cardiovascular morbidity is due to the cancer or its treatment, or a shared risk factor for DTC and cardiovascular morbidity.

In conclusion, we found that the survival rate of patients diagnosed with a DTC is excellent, but the risk of cardiovascular diseases is increased among patients treated for DTC, compared with age- and gender-matched controls. The increased risk is mostly accountable to an increased risk of atrial fibrillation. The patients with a low mean TSH level (<0.1 mU/l) have an increased risk of CVD. While the study rises concerns about the long-term cardiovascular effects of THST-induced iatrogenic thyrotoxicosis, the optimal level of TSH remains to be settled in future studies.

Conflict of interest

The authors have no conflict of interest to declare

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Figure legends

Figure 1 The number of the study subjects and their hospital visits associated with cardiovascular diseases.

Figure 2 Cumulative morbidity due to all cardiovascular diseases, all arrhythmias and atrial fibrillation in patients treated for differentiated thyroid cancer, compared with the matched control group (log-rank test).

Figure 3 All-cause mortality and cardiovascular mortality in the patients treated for differentiated thyroid cancer, compared with the matched control group (log-rank test).

Figure 4 Cumulative cardiovascular morbidity by the mean TSH level (panels a-c) and by the cumulative radioiodine dose (panels d-f) in the DTC patients compared to the respective control group (log-rank test).

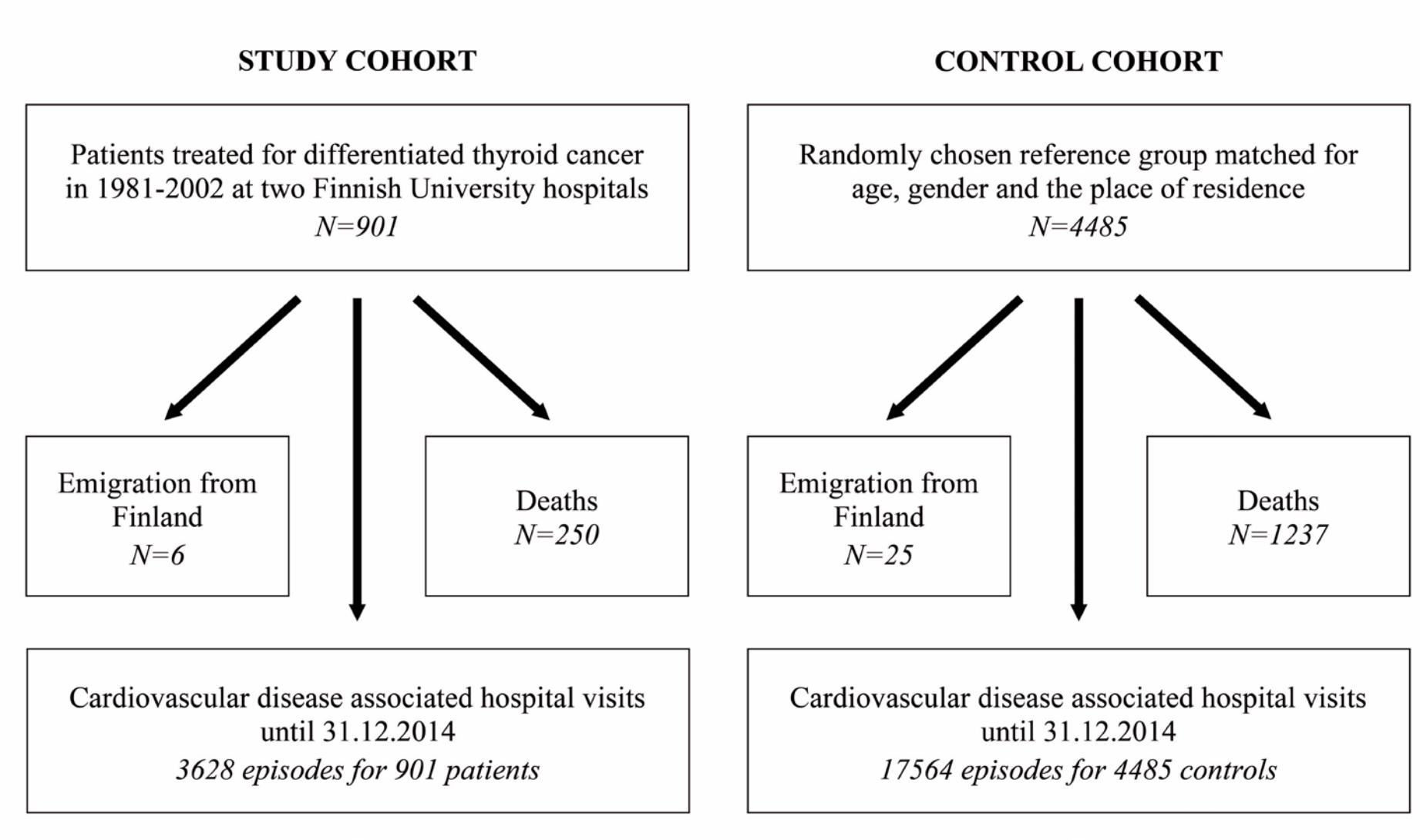
STUDY COHORT
Patients treated for differentiated thyroid cancer in 1981-2002 at two Finnish University hospitals
N=901
Emigration from Finland
N=6
Deaths
N=250
Cardiovascular disease associated hospital visits until 31.12.2014
3628 episodes for 901 patients
CONTROL COHORT
Randomly chosen reference group matched for age, gender and the place of residence
N=4485
Emigration from Finland
N=25
Deaths
N=1237
Cardiovascular disease associated hospital visits until 31.12.2014
17564 episodes for 4485 controls

Figure 1

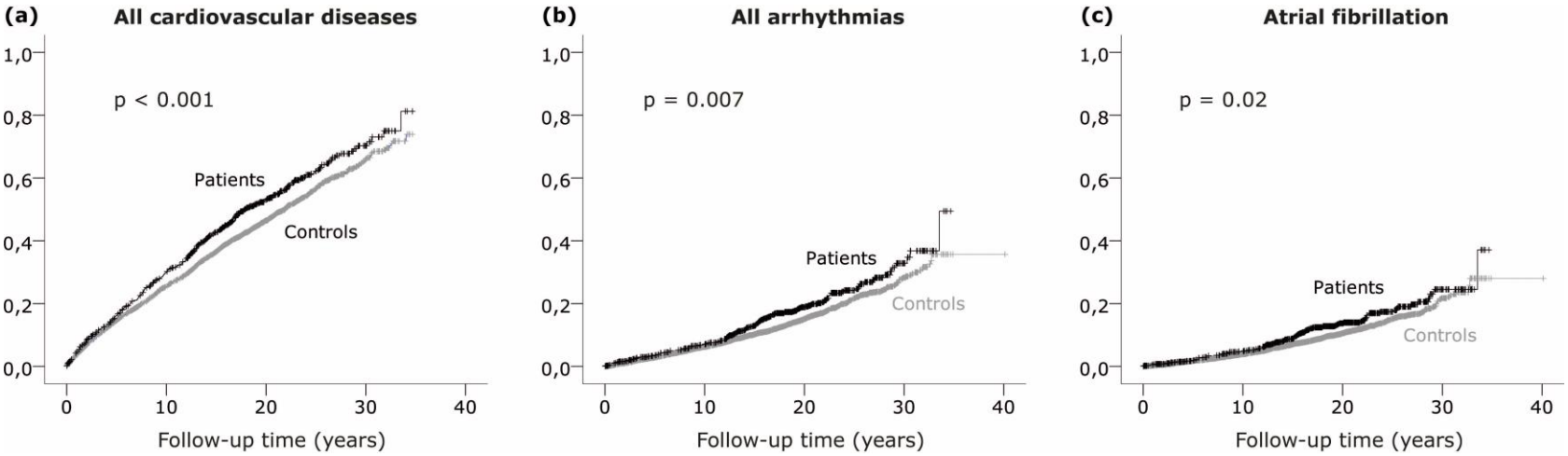

Figure 2

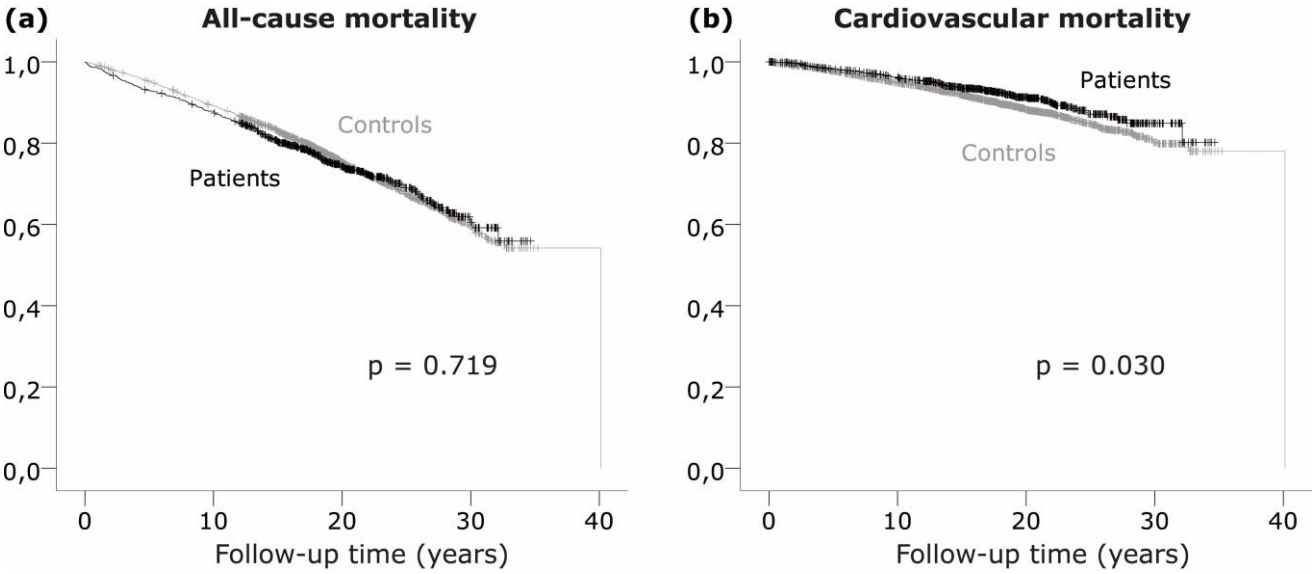

Figure 3

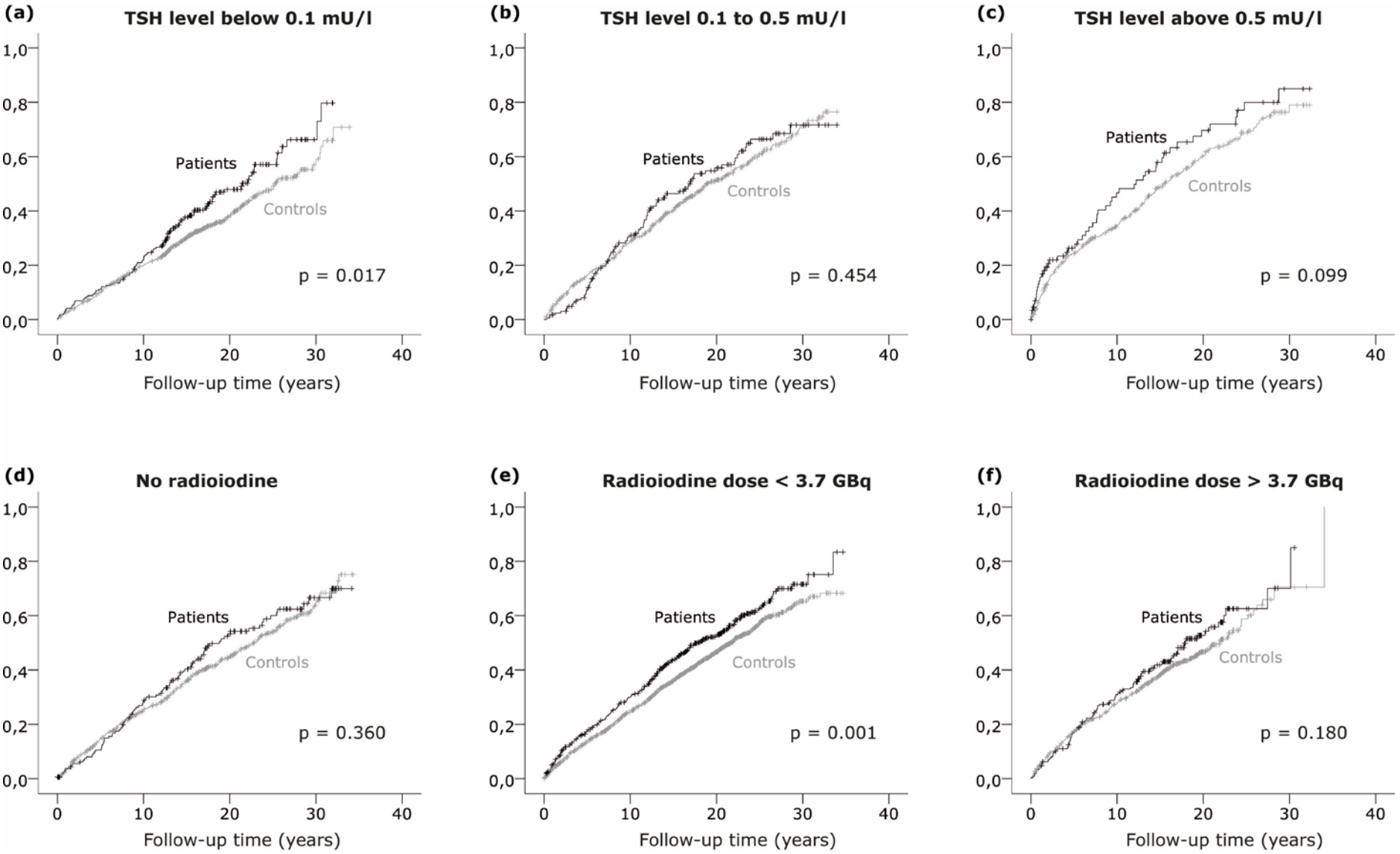
(a)
TSH level below 0.1 mU/l
Patients
Controls
p = 0.017
(b)
TSH level 0.1 to 0.5 mU/l
Patients
Controls
p = 0.454
(c)
TSH level above 0.5 mU/l
Patients
Controls
p = 0.099
(d)
No radioiodine
Patients
Controls
p = 0.360
(e)
Radioiodine dose < 3.7 GBq
Patients
Controls
p = 0.001
(f)
Radioiodine dose > 3.7 GBq
Patients
Controls
p = 0.180
1,0
0,8
0,6
0,4
0,2
0,0
0
10
20
30
40
Follow-up time (years)

Figure 4

Table 1. General information and follow-up times for the patients treated for differentiated thyroid cancer and the randomly chosen control group[a].

	Patients (n=901)	Controls (n=4485)
Age, mean (SD)	48.8 (15.9)	48.7 (15.8)
Gender, female (%)	733 (81%)	3650 (81%)
Follow-up time, years, median, (IQR)	18.8 (14.4-23.5)	19.0 (15.1-23.4)
Pathology		
PTC[b]	709 (79%)	-
PTC[b] follicular variant	95 (11%)	-
FTC[c]	97 (11%)	-
TSH level[d], mU/l, median, (IQR)	0.11 (0.05-0.35)	-
below 0.1 mU/l	215 (46%)	-
0.1 to 0.5 mU/l	165 (35%)	-
above 0.5 mU/l	89 (19%)	-
RAI[e] treatment, GBq, median, (IQR)	3.7 (3.7-6.9)	-
No RAI	169 (19%)	-
below 3.7 GBq	522 (58%)	-
above 3.7 GBq	210 (23%)	-

[a]The patients and the controls were matched for age, gender and the place of residence.
[b]*PTC* papillary thyroid cancer, [c]*FTC* follicular thyroid cancer
[d]Geometric mean of all available TSH measurements after the diagnosis of thyroid cancer, available from 469 patients
[e]*RAI* radioiodine treament

Table 2. Cardiovascular morbidity of patients treated for differentiated thyroid cancer (DTC) compared with a control group matched for age, gender and the place of residence.

	Hospital visits		Patients *vs.* controls	
Cardiovascular disease	Patients (n=901)	Controls (n=4485)	Hazard ratio[a] (CI)	P value
All cardiovascular diseases	478	2134	1.16 (1.05-1.28)	0.004*
Hypertension	210	914	1.16 (0.99-1.34)	0.060
All arrhythmias	170	693	1.25 (1.06-1.48)	0.008*
Atrial fibrillation	120	485	1.29 (1.06-1.57)	0.013*
Diseases of arteries and veins	172	774	1.12 (0.95-1.32)	0.193
Coronary artery disease	145	786	0.94 (0.78-1.12)	0.457
Cerebrovascular diseases	84	440	0.98 (0.78-1.24)	0.865
Heart failure	61	383	0.77 (0.59-1.01)	0.054
Valvular diseases and cardiomyopathies	38	151	1.26 (0.88-1.79)	0.213
Diseases of pulmonary arteries	24	83	1.48 (0.94-2.33)	0.091

[a]Adjusted for prevalent cardiovascular morbidity prior to the diagnosis of DTC (Cox regression analysis)
*Statistically significant difference between the patients and the controls

Table 3. Mortality from different cardiovascular diseases in patients treated for differentiated thyroid cancer (DTC) compared with a control group matched for age, gender and the place of residence.

Cause of death	Deaths		Patients *vs.* controls	
	Patients (n=901)	Controls (n=4485)	Hazard ratio[a] (CI)	P value
All deaths	250	1237	0.98 (0.85-1.12)	0.754
Cardiovascular deaths	81	533	0.73 (0.58-0.92)	0.008*
Hypertension	5	12	1.93 (0.68-5.51)	0.219
All arrhythmias	4	13	1.52 (0.50-4.67)	0.463
Atrial fibrillation	3	12	1.24 (0.35-4.40)	0.740
Diseases of arteries and veins	10	36	1.39 (0.69-2.79)	0.362
Coronary artery disease	42	315	0.69 (0.50-0.95)	0.023*
Cerebrovascular diseases	16	119	0.69 (0.41-1.16)	0.161
Heart failure	3	10	1.40 (0.38-5.11)	0.110
Valvular diseases and cardiomyopathies	0	21		0.970
Diseases of pulmonary arteries	1	4	1.29 (1.44-11.55)	0.820

[a]Adjusted for prevalent cardiovascular morbidity prior to the diagnosis of DTC (Cox regression analysis)
*Statistically significant difference between the patients and the controls